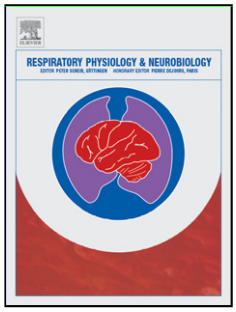
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Sex, stress and sleep apnoea: Decreased susceptibility to upper airway muscle dysfunction following intermittent hypoxia in females

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Highlights

Obstructive sleep apnoea syndrome (OSAS) is very common and more prevalent in men than women.

Sex differences in the intrinsic control and inherent collapsibility of the upper airway partly explain female advantage.

Chronic intermittent hypoxia (CIH) is a dominant feature of OSAS due to recurrent apnoea. CIH-induced upper airway muscle dysfunction is sex-dependent, exacerbated by ovariectomy and ameliorated by oestrogen replacement therapy.

Female advantage extends to intrinsic properties of upper airway muscles and resilience to redox stress, likely mediated by oestrogen receptor α signalling.

The oestrogen-oestrogen receptor α axis is a potential target in the treatment of OSAS, especially in post-menopausal women.

Abstract

Obstructive sleep apnoea syndrome (OSAS) is a devastating respiratory control disorder more common in men than women. The reasons for the sex difference in prevalence are multifactorial, but are partly attributable to protective effects of oestrogen. Indeed, OSAS prevalence increases in post-menopausal women. OSAS is characterized by repeated occlusions of the pharyngeal airway during sleep. Dysfunction of the upper airway muscles controlling airway calibre and collapsibility is implicated in the pathophysiology of OSAS, and sex differences in the neuro-mechanical control of upper airway patency are described. It is widely recognized that chronic intermittent hypoxia (CIH), a cardinal feature of OSAS due to recurrent apnoea, drives many of the morbid consequences characteristic of the disorder. In rodents, exposure to CIH-related redox stress causes upper airway muscle weakness and fatigue, associated with mitochondrial dysfunction. Of interest, in adults, there is female resilience to CIH-induced muscle dysfunction. Conversely, exposure to CIH in early life, results in upper airway muscle weakness equivalent between the two sexes at 3 and 6 weeks of age. Ovariectomy exacerbates the deleterious effects of exposure to CIH in adult female upper airway muscle, an effect partially restored by oestrogen replacement therapy. Intriguingly, female advantage intrinsic to upper airway muscle exists with evidence of substantially greater loss of performance in male muscle during acute exposure to severe hypoxic stress. Sex differences in upper airway muscle physiology may have relevance to human OSAS. The oestrogen-oestrogen receptor α axis represents a potential therapeutic target in OSAS, particularly in post-menopausal women.

Key words: Antioxidant; Intermittent hypoxia; Oestrogen; Oestrogen receptor α; Sleep apnoea

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1. Obstructive sleep apnoea syndrome: Neurogenic and myogenic mechanisms contributing to upper airway collapse

The human pharynx is a compliant, collapsible segment of the conducting airways. The muscular conduit is vulnerable to occlusion, especially during inspiratory effort when sub-atmospheric pressures are generated by contraction of the muscles of inspiration, principally the diaphragm, necessary for effective ventilation of the lungs. The respiratory-related activation of several complementary muscles serves to control airway calibre and stability during basal breathing, and in response to dynamic challenges such as hyperventilation or hyperpnoea (White, 2005; White & Younes, 2012; Jordan et al., 2014). Reflex activation of upper airway muscles defends airway patency by dilating and/or stiffening the conducting airway, decreasing pharyngeal compliance and resistance to airflow, thereby facilitating the cyclical bulk flow of air essential for gas exchange between the lungs and the environment (White & Younes, 2012; Jordan et al., 2014; Carberry et al., 2015). Pharyngeal dilator muscle recruitment is critical in the recovery of a collapsed airway segment (Remmers et al., 1978; White, 2005), which can present during sleep when airway muscle hypotonia, arising from decreased motoneuron drive especially in REM sleep (McSharry et al., 2014), results in airway narrowing and an increased propensity for airway occlusion at one or more sites along the length of the pharynx. Repeated sleep-dependent occlusions of the upper airspace, with disruption to pulmonary airflow and resultant arterial blood gas derangements, is the hallmark signature of the obstructive sleep apnoea syndrome (OSAS), the most common form of sleep-disordered breathing (Dempsey et al., 2010; White & Younes, 2012; Jordan et al., 2014). Airway collapse results in arousal from sleep (Basner et al., 1992; Kimoff, 1996; Horner et al., 1998), which is typically required to reactivate cranial neuro-mechanical mechanisms governing control of airway calibre (Remmers et al., 1978; Kimoff et al., 1997; White, 2005; Jordan et al., 2011; White & Younes, 2012). The recurrent cycle of airway collapse and recovery is disruptive to sleep architecture and manifests the cardinal symptom of OSAS, namely daytime sleepiness.

The causes and drivers of OSAS are multifactorial, but the intrinsic collapsibility of the pharynx is likely the major predisposing factor in the pathogenesis of OSAS (Eckert et al., 2009). Neurogenic and myogenic mechanisms are implicated, culminating in ineffectual control of airway patency in individuals predisposed to airway collapse during sleep typically owing to congenital and/or acquired aberrant airway anatomy. Because the pharynx lacks bony support, airway calibre is critically dependent upon the activity of dilator muscles (Schwartz et al., 1998; White, 2005; White & Younes, 2012). Much attention has been directed towards an understanding of the sleep-related withdrawal of cranial motor drive to the muscles of the upper airway (Grace et al., 2013; Horner et al., 2014) with consequential reductions in upper airway muscle tone (White, 2005; Carberry et al., 2016), which

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together with impaired responsiveness of upper airway dilators to reflex activation during sleep (Wheatley et al. 1993; Shea et al. 1999), conspire to increase the likelihood of airway obstructive events, common in those patients predisposed to airway collapse. Hypotonia in rapid-eye movement sleep, when there is a dramatic change in cranial motor nervous output, is a trigger of apnoeic events (Schwartz et al., 1998; White & Younes, 2012), but interestingly the magnitude of the loss of genioglossus activity does not differ between normal healthy and OSAS patients and is not different between men and women, suggesting that aberrant mechanics in the context of a generalized sleep-related loss of motor drive is the predisposing factor for airway collapse (Eckert et al., 2009).

Thus, there is a growing appreciation that alterations in the intrinsic mechanical properties of the soft tissue structures of the pharynx including the upper airway dilator muscles, the final effectors of neuro-mechanical coupling, are likely important contributors to the pathophysiology of OSAS. Indeed, poor airway mechanics can prevail in OSAS patients who appear to show adequate dilator muscle responsiveness, as determined by electromyogram recordings (Eckert and Wellman, 2015), and OSAS patients may be at risk of increased upper airway muscle fatigue (Eckert et al., 2011). Structural changes in upper airway muscles of OSAS patients, including fibre type transitions (Stauffer et al., 1989; Smirne et al. 1991; Series et al., 1995, 1996a,b; Ferini-Strambi et al., 1998; Carrera et al., 2004) and altered metabolic activity (Series et al., 1995; Kim et al., 2014) are reported, consistent with evidence of altered isolated muscle function (Series et al., 1995, 1996a,b, 1999; Carrera et al., 1999, 2004). Inflammation and myopathy (Boyd et al., 2004; Kimoff et al., 2011) have been described in upper airway muscle biopsies from OSAS patients, with evidence too of neuropathic sensorimotor injury in OSAS (Svanborg 2005; Saboisky et al., 2012). Moreover, upper airway muscle functional deficits correlate with airway collapsibility in patients with OSAS (Series et al., 1996a, 2006). These findings have led to the hypothesis that upper airway muscle dysfunction in OSAS increases susceptibility to airway collapse, and/or leads to impaired capacity to recover an occluded airway during sleep, thereby establishing an inescapable spiral of disability perpetuating the condition (Petrof et al., 1996; Bradford et al., 2005; Kimoff 2007; O'Halloran, 2016).

2. Sex differences in the prevalence of OSAS: Are sex differences in upper airway muscle performance relevant to the pathophysiology of OSAS?

Whatever the underlying mechanism(s) giving rise to OSAS, the widespread devastating consequences of the respiratory control disorder are alarming. Sleep apnoea is an independent risk factor for premature death (Putcha et al., 2016), with a wealth of evidence pointing to OSAS-related

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cardio-metabolic and neurocognitive dysfunction (McNicholas et al., 2007; Younes & White, 2012). OSAS is very common (Young et al., 1993; Seneratna et al., 2016), but two to three times more prevalent in men than women (Young et al., 1993; Seneratna et al., 2016). Considering the high prevalence of sleep-disordered breathing in the general population, which is on the rise (Peppard et al., 2013), and the association between OSAS and major life-threatening co-morbidities (Nieto et al., 2009; Young et al., 2008; Hla et al., 2015; Korcarz et al., 2014), one can readily appreciate why OSAS is regarded as a major public health issue. Age, obesity and male sex are noteworthy independent risk factors for the development of OSAS (Young et al., 1993; Seneratna et al., 2016). The inter-relationship between these risk factors, upper airway mechanics, and susceptibility to the development of sleep apnoea has been established (Kirkness et al., 2008). Fundamental differences in airway anatomy and airway tissue mechanics appear pivotal to sex-related differences (Pillar et al., 2000). Women have smaller diameter airways even when matched for lung volume (Guenette et al., 2009). There is no difference in pharyngeal resistance between men and women until the onset of slow wave sleep at which time pharyngeal resistance is increased in men (Trinder et al., 1997). The increased pharyngeal resistance response to inspiratory loading is also greater in men (Pillar et al., 2000). Men have increased pharyngeal length (Malhotra et al., 2002) and more collapsible airways (Jordan et al. 2005; Squier et al., 2010) than women, which increases risk of developing OSAS in men compared with women, although Rowley et al., (2001) reported no sex difference in critical closing pressure in young healthy subjects. Differences in OSAS severity between sexes may be partly related to greater upper airway responses to airway obstruction in females compared with males, when matched for passive airway properties (Chin et al., 2012), although other data is incongruent with this conclusion (Pillar et al., 2000). Genioglossus electromyogram activity is greater in females compared with males (Popovic & White 1995), but the biomechanical behaviour of the upper airway cannot be easily predicted from electromyographic recordings (Bliston & Gandevia 2014).

Tongue strength is predictive of airway patency in OSAS (Kanezaki et al., 2015), and lower tongue stiffness (Brown et al., 2015) and increased fatigue (McSharry et al., 2012) are observed in OSAS patients, but little is known concerning potential sex differences in OSAS notwithstanding that tongue protrusion force and fatigue are equivalent in healthy males and females (Mortimore et al., 1999), with weakness evident in ageing in both sexes (Mortimore et al., 1999). Upper airway muscle contractile and endurance properties have been comprehensively examined in rodent models and are equivalent in naïve males and females (Cantillon & Bradford, 1998, 2000; Skelly et al., 2012a; Lewis et al., 2016). As such, inherent differences between sexes in upper airway muscle functional properties, has not generally been considered as potentially relevant to the pathophysiology of

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OSAS. However, recent evidence in animal models revealing sex-related differences in upper airway muscle responses to hypoxic stress (Skelly et al., 2012a; Lewis et al., 2016), changes this perspective with potential relevance to OSAS (discussed below). Whereas the prevalence and severity of OSAS is lower in women, the consequences of the disease are similar or arguably worse than in male counterparts (Won & Guilleminault, 2015). Menopausal status, especially transition to menopause, puts women at increased risk of developing OSAS (Young et al., 2003). Given strong evidence of sexual dimorphism in the control of breathing (Tatsumi et al., 1997; Zabka et al., 2001; Behan et al., 2002; Wenninger et al., 2009; Kinkead et al., 2013; Syed et al., 2013) resulting from the influential role of sex hormones at multiple sites of the respiratory control system, it is perhaps not surprising that the decline in ovarian hormones at menopause poses a threat to respiratory homeostasis, including challenges for upper airway stability (Young et al., 2003), compounded by the deleterious influences of ageing *per se* on upper airway mechanics. The loss of the protective effects of oestrogen on muscle redox homeostasis in the peri-menopausal period could put women at increased risk of upper airway muscle dysfunction, which might negate female advantage in terms of control of airway calibre (Jordan et al. 2005; Squier et al., 2010).

3. Chronic intermittent hypoxia is a dominant feature of OSAS driving morbidity

Redox biology is central to OSAS. The disorder is characterized by exposure to recurrent cyclical bouts of hypoxia and re-oxygenation, due to repeated obstructions of the upper airway that interrupt pulmonary airflow: OSAS is an oxidative stress disorder (Lavie, 2003). Notwithstanding the multifactorial nature of the complex respiratory condition, there is a general consensus within the field that exposure to chronic intermittent hypoxia, typifying OSAS, is injurious to many tissues (Jun et al. 2008; Chopra et al., 2016; O'Halloran, 2016). Indeed, animal models of CIH recapitulate many of the morbidities reported in OSAS patients, thereby serving as a useful model of the disease (Chopra et al., 2016; O'Halloran, 2016). There is strong evidence that CIH alters cardiorespiratory control, through adverse actions at multiple sites in the integrative control network (Peng et al., 2003, 2006, 2014; Rey et al., 2004; Julien et al., 2008; Del Rio et al., 2010; Moraes et al., 2013; Zanella et al., 2014; Moraes & Machado, 2015; Garcia et al., 2016), disrupting the rhythm and pattern (Edge et al., 2012a, 2014; Zanella et al., 2014; Garcia et al., 2016) of central respiratory drive, with evidence of increased propensity for central apnoea following CIH exposure (Edge et al., 2012b; Donovan et al., 2014; Souza et al., 2015), potentially compounding OSAS (O'Halloran, 2016). With relevance to the control of upper airway calibre, several groups have independently shown that CIH impairs upper airway muscles and their neural control. CIH impairs respiratory motor responsiveness to excitatory drive (O'Halloran et

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al., 2002; Veasey et al., 2004; Edge et al., 2014), resulting in increased upper airway collapsibility (Ray et al., 2007). Beyond neurogenic changes, CIH has deleterious effects on upper airway muscle physiology, with evidence of upper airway muscle weakness and fatigue following exposure to CIH (McGuire et al., 2002a,b; Pae et al., 2005; Dunleavy et al., 2008; Li & Liu, 2009; Liu et al., 2009; Jia & Liu, 2010; Huang & Liu, 2011; Ding & Liu, 2011; Skelly et al., 2012a; Wang et al., 2013; Lu et al., 2014). Fibre type transitions have been described in some studies (Pae et al., 2005; Liu et al., 2009), but it appears that upper airway muscle dysfunction is not dependent on fibre-type remodelling or atrophy (Skelly et al., 2012a), phenotypic differences that are perhaps dependent on the experimental paradigm employed in the studies, which varies considerably in terms of pattern, duration and intensity of hypoxic exposure. An increase in the proportion of fast fatiguable 2B fibres was observed by Pae et al. (2005), consistent with observations of decreased muscle endurance (Pae et al., 2005), a finding which resonates with observations of slow-to-fast fibre transitions in OSAS (Series et al., 1995, 1996a,b), and increased relative area of fast fibres in an upper airway muscle of the English bulldog (Petrof et al., 1994), a model of OSAS. Upper airway muscle dysfunction is dependent on the duration of exposure to CIH, illustrating the cumulative deleterious nature of CIH-related stress in respiratory muscle (Pae et al., 2005; Shortt et al., 2014), which may be NADPH oxidase-dependent (Williams et al., 2015). When extended for several weeks of exposure, CIH can also increase upper airway muscle fatigue and delay recovery from fatigue (McGuire et al., 2002a,b). CIH increases genioglossus fatigue (Liu et al., 2009; Jia & Liu, 2010; Huang & Liu, 2011; Ding & Liu, 2011; Wang et al., 2013; Lu et al., 2014; Li & Liu, 2009), which may be HIF-1α-dependent (Jia & Liu, 2010; Ding & Liu, 2011), and related to mitochondrial dysfunction (Zhang et al., 2010; Huang et al., 2012, 2014). CIH increases endoplasmic reticulum stress and apoptotic signalling (Zhang et al., 2013), with evidence of aberrant sub-cellular structural remodelling (Huang et al., 2012; Zhang et al., 2010), although only modest cellular oxidative stress has been noted in some models (Williams et al., 2015). The pivotal role of redox signalling in CIH-induced upper airway dysfunction is revealed by antioxidant intervention studies, which ameliorate or prevent CIH-induced aberrant changes in respiratory muscle (Dunleavy et al., 2008; Skelly et al., 2012a; Shortt et al., 2014).

4. CIH-induced upper airway muscle dysfunction is sex-dependent, exacerbated by ovariectomy and ameliorated by oestrogen replacement therapy

There is emerging evidence to suggest that the effects of exposure to CIH on upper airway muscle function are age-dependent. Skelly et al. reported CIH-induced upper airway muscle weakness in adult (Skelly et al., 2012a), but not middle-aged rats (Skelly et al., 2012b), the latter finding consistent with

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a report showing no fibre type or functional effects of CIH on upper airway muscle in middle-aged Zucker rats (Ray et al., 2007). However, there is increased susceptibility to CIH in early life. A modest CIH paradigm producing no discernible effect on upper airway muscle contractile properties in adult animals resulted in persistent upper airway muscle weakness when exposure to CIH occurred during neonatal development (McDonald et al., 2015), an effect also associated with increased susceptibility to a subsequent bout of exposure to CIH in adulthood (McDonald et al., 2016).

Surprisingly, in the light of sex-related differences in the prevalence and manifestation of OSAS (Young et al., 1993; Seneratna et al., 2016), and the wealth of evidence indicative of sex differences in the response of various homeostatic systems to stressors, there is a dearth of information comparing homeostatic system responses to CIH challenge between the sexes. Of interest, exposure to CIH causes hypertension in female rats equivalent in magnitude to that occurring in males (Souza et al., 2015). The latter is somewhat surprising in the light of oestrogen's antioxidant actions (Borrás et al., 2003; Pajovic & Saicic, 2008), given the evidence that CIH-induced hypertension is redox-dependent. Altered cardio-respiratory coupling following exposure to CIH is observed in both sexes, but interestingly the aberrant signature differs between the sexes (Souza et al., 2016). Concerning the issue of sex-related susceptibility to airway collapsibility, CIH-induced pharyngeal dilator muscle weakness was observed in male but not female rats in a model of moderate sleep-disordered breathing (Skelly et al., 2012a). The putative role of sex hormones is inferred from observation that whilst female upper airway muscle shows an apparent resilience to CIH-related stress when exposed during adulthood, CIH exposure during neonatal development causes upper airway muscle weakness, which is equivalent in young males and females studied at 3 and 6 weeks of age (McDonald et al., 2016).

Longer-lasting exposures to CIH (35 days compared with 9 days in Skelly et al., 2012a) cause genioglossus dysfunction in female rats (Liu et al., 2009; Huang & Liu, 2011; Lu et al., 2014; Li & Liu, 2009), but interestingly, CIH-induced upper airway muscle dysfunction is exacerbated in ovariectomized females (Liu et al., 2009; Huang & Liu, 2011), and partially ameliorated by oestrogen replacement therapy (Liu et al., 2009; Jia & Liu, 2010), which is also effective in restoring CIH-induced HIF-1α levels (Jia & Liu, 2010) and decreased SERCA activity (Liu et al., 2009). Phytoestrogens, particularly genistein, improves upper airway muscle function in ovariectomized females exposed to CIH (Huang & Liu, 2011), associated with muscle upregulation of oestrogen receptor β (Li & Liu, 2009), though the effects may be unrelated to oestrogenic actions (Huang & Liu, 2011). Genestein also attenuates upper airway muscle fatigue in male rats (Ding & Liu, 2011; Zhou & Liu, 2013), which may be HIF-1α-dependent (Zhou & Liu, 2013). Thus it appears that oestrogen-dependent signalling affords

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protection in upper airway muscle response to CIH-related stress. Oestradiol, via oestrogen receptor α receptors, increases upper airway muscle performance (Hou et al., 2010) and alters upper airway muscle fibre types (Guo et al., 2014), and the steroid provides the best protection to upper airway muscle endurance in ovariectomized females exposed to CIH, via elevated muscle oestrogen receptor α levels (Lu et al., 2014). Given the robust capacity for antioxidant supplementation to prevent or reverse CIH-induced upper airway muscle weakness (Skelly et al., 2012a), the beneficial effect of oestrogen likely relates to enhanced cellular antioxidant defence (Borrás et al., 2003). Mitochondrial dysregulation and oxidative stress are observed in female skeletal muscle when oestrogen receptor α expression is knocked out (Ribas et al., 2011) or blocked (Baltgalvis et al., 2010). The sub-cellular stress in CIH-exposed upper airway muscles (Zhang et al., 2010, 2013; Huang et al., 2012, 2014), suggests that the protective effects of oestrogen relate to actions at the level of the mitochondria (Borrás et al., 2003), pivotal to muscle aerobic performance. We posit that this could also conceivably extend to putative effects at the level of the muscle contractile apparatus, but little is known about this at this time.

5. Does oestrogenic signalling confer female advantage in upper airway muscle response to redox stress?

Considering the beneficial effects of oestrogen in muscle homeostasis, withdrawal of oestrogen signalling in menopausal women and animal models of ovariectomy contributes to muscle dysfunction and increased susceptibility to oxidative stress. This is likely very relevant to the physiological control of upper airway patency in postmenopausal women, particularly during transition, and could be associated with an acute loss of female advantage in terms of upper airway mechanics (Pillar et al., 2000; Jordan et al. 2005; Squier et al., 2010), providing a substrate for airway collapse, re-balancing the gender divide in terms of OSAS prevalence compared with age-matched males. Oestrogen replacement therapy holds some promise (Bixler et al., 2001), though this is currently under renewed interpretation owing to evidence of a healthy user bias (Mirer et al., 2016).

Higher levels of oestrogen confer advantage to females compared with males in respect of skeletal muscle endurance (Hunter, 2016), although this is likely influenced too by effects of male hormones. However, surprisingly, an absence of sex differences is consistently reported for contractile and endurance properties of upper airway muscles in humans and animal models (Cantillon & Bradford 1998, 2000; Skelly et al., 2012a; McDonald et al., 2015; Lewis et al., 2016). Considering the beneficial effects of oestrogen, and the clear detrimental effects of its withdrawal in female upper airway muscle

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(Liu et al., 2009; Huang & Liu, 2011), it is interesting to consider that male upper airway muscle is capable of matching female performance under control conditions, perhaps related to basal oestrogen-mediated mitochondrial maintenance amongst other factors. Female advantage intrinsic to upper airway muscle is revealed however in response to stress. In rat (Skelly et al., 2012a) and mouse (Lewis et al., 2016) upper airway muscle, there was a significantly greater loss of performance in response to acute severe hypoxic stress in male muscle compared with female muscle, consistent with suggestions that oestrogen primes mitochondrial resilience to stress (Borrás et al., 2003). Sex differences are observed in human limb muscle response to chronic hypoxia (Fulco et al., 2001) and in neurons in response to intermittent hypoxia-related oxidative stress (Sanfilippo-Cohn et al., 2006). The implications are that female advantage in terms of upper airway mechanics may be twofold: first, the intrinsic stability of the female airway is greater than in males (Pillar et al., 2000; Jordan et al. 2005; Squier et al., 2010), and second, female upper airway muscle tolerance of stress is enhanced compared with males (Skelly et al., 2012a; Lewis et al., 2016) serving a protective role in the event of pathophysiological perturbation to respiratory control. The observation is intriguing given that oestrogen receptor α expression is equivalent in male and female muscle (Lemoine, 2003), though muscle specific differences are plausible. Further comparison between sexes of upper airway muscle performance in response to stressors in health and disease is warranted. The importance of oestrogenic signalling influencing fibre type transitions in OSAS was recently revealed (Chen et al., 2016), once again highlighting the potential therapeutic application of hormone replacement therapy, especially in post-menopausal women. It should be acknowledged however that not all women go on to develop sleep-disordered breathing in the menopausal transition, which illustrates the complex multifactorial nature of sleep-related upper airway collapse. A greater understanding of those additional factors and their interplay, which act to predispose females to the development of OSAS in the post-menopausal period will help identify those cohorts that are at increased risk of poor airway control during oestrogen withdrawal potentially ensuring early interventional therapy.

6. Summary and perspective: oestrogen replacement as a therapy in OSAS?

OSAS is a devastating disorder more common in men than women. Female advantage in terms of airway control principally relates to intrinsic features of the upper airway, perhaps including the physiology of upper airway muscles. There is increased susceptibility to hypoxic stress in upper airway muscles of males and ovariectomized females with implications for the pathophysiology of OSAS. We posit that the withdrawal of oestrogen in the peri-menopausal transition may be detrimental to female upper airway muscle response to hypoxic stress, at a time when age-related changes in the

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control of airway calibre, including function of the upper airway muscles, increases the risk of obstructive airway events that give rise to intermittent hypoxia. Combined, these factors contribute to increased risk of developing OSAS. Oestrogen replacement therapy holds promise as a therapeutic strategy. Antioxidant interventions are also potentially useful adjunctive therapies ameliorating redox stress arising from intermittent hypoxia due to recurrent apnoea. There are gaps in the understanding of sex differences in upper airway muscle biology that warrant attention.

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